REMARKS

Rejections Under 35 U.S.C. § 103(a)

The Examiner maintained the rejection of claims 1-12 under 35 U.S.C. § 103 as unpatentable over US patent 4,740,374 or US patent 5,866,157, individually or combined with US patent 5,271,946. Applicant respectfully requests reconsideration based on the previously submitted arguments regarding criticality of particle size limitation and, furthermore, based on the insufficiency of the teachings of the cited prior art, particularly the '946 patent.

The Examiner states that sodium acetate is known as a powder and that "Applicants failed to show superior and unexpected results that show criticality in the claimed particle sizes." The Examiner further states that "It is within the skill in the art to determine the diameter of the particle in order to achieve a beneficial effect." (Page 5 of the Office Action).

Applicant Provided Results Demonstrating Criticality of the Particle Size

Applicant respectfully request that the Examiner consider the following superior and unexpected results in the specification that indicate there is a critical size of particles in the claimed invention to achieve the desired permeability due to a sufficient ion-pair formation (page 7, lines 15-17 of the specification). In particular, on page 4 of the specification Applicant stated (emphasis added):

> "During extensive researches to solve these problems the inventors found out that comprising an organic acid salt of a particular particle size in adhesive preparations containing a base drug as a salt form improves solubility of the drug to skin via an ion-pair formation, and that it significantly improves skin permeability of the drug by enhancing partition coefficient to skin, and thus accomplished the invention. Specifically, in case of the mean diameter of a base drug and an organic acid salt contained was 100μm or less (this particle size indicates volume average particle size when measured by the use of a particle fineness analyzer) the effect was observed. Particularly, it was revealed that in a fat-soluble base, though the solubility of a drug and an organic acid salt was so bad they remain as powder in the preparation, percutaneous absorbance of the drug was greatly affected by the size of the particle diameter of the organic acid salt. In particular, as an organic acid salt, the effect of sodium acetate is high, and

in this case the average particle size of 0.1-10μm shows extremely excellent percutaneous drug-absorbance promoting effect."

Applicant also provided examples of the preparation of compositions with particle sizes of organic acid salt less than 100 μm for forming a sufficient ion-pair formation. Comparative examples in which the particle sizes of organic acid salt were greater than 100 μm also were provided. When compositions of these two kinds were subjected to a skin permeability test on hairless mice, the results (shown in Figures 1-3) demonstrate that the compositions having particle size of less than 100 μm were superior since a sufficient ion-pair formation was formed (page 7, lines 15-17 of the specification), with a marked criticality corresponding to the size of the particles used in the compositions.

Therefore, Applicant's specification clearly indicates that the particle size range for forming a sufficient ion-pair formation is unexpectedly critical for skin permeability of the claimed compositions.

The Prior Art Does Not Provide a Teaching of Organic Acid Powder Particles of the Correct Size in Percutaneous Absorption Adhesive Preparations

The Examiner admits that the '374 patent and the '157 patent "do not disclose the organic acid in the powder form or the mean diameter of the powder particles." (See page 4 of the Office Action). The Examiner alleges that the '946 patent teaches sodium acetate having a particle size of about 0.1 to 200 μm, thereby providing the missing element of the presently claimed invention. Applicant respectfully disagrees for the following reasons.

The '946 patent relates to providing controlled release forms of azelastine, which can be obtained through one of four ways: (1) binding of azelastine to physiologically acceptable cation exchangers (beginning at col. 3, line 29); (2) coating of azelastine particles, granulate or pellet grains or azelastine-containing tablets with coatings of various compounds (beginning at col. 3, line 63); (3) coating tablets pressed disks, etc. of azelastine and one or more osmotically active substances with a semi-permeable membrane (beginning at col. 5, line 9); and (4) embedding or

binding azelastine with fats or polymers (beginning at col. 7, line 3), none of which are sodium acetate.

Regarding the binding to cation exchangers, sodium acetate is not a cation exchanger. Regarding the coating of azelastine particles, none of the compounds mentioned as coating agents are sodium acetate, nor would coatings be comprised of particles of sodium acetate.

Regarding the coated tablets, sodium acetate is not used in the coating, and thus is not used in a manner equivalent to Applicant's invention. Instead, the '946 patent provides that sodium acetate is a pore forming agent. As defined by the '946 patent, "the term pore forming agent, as applied both to solids and to liquids comprises substances which can be dissolved, extracted or leached out of liquid present in the coating used from the precursor of the microporous membrane with the formation of an effective, open cellular microporous layer." (Col. 6, lines 52-57). The sodium acetate is used to create a porous layer by leaching out of the coating, and therefore it is not part of the porous layer.

Thus the Examiner's assertion that the '946 patent teaches a pharmaceutical composition comprising sodium acetate having a particle size of about 0.1 to 200 micrometers is simply incorrect, for two reasons. First, the pharmaceutical composition does not have a particle size of about 0.1 to 200 micrometers; the '946 patent teaches that "The pore forming solids have a particle size of about 0.1 to 200 μm." (Col. 6, lines 58-59). Therefore, it is the pore forming agent solid (e.g., sodium acetate) that has the size shown by Applicant to have unexpected properties. As noted above, the pore forming agents are "dissolved, extracted or leached" out of the coating and therefore are not present in the particles. Thus, they cannot form an ion-pair formation in the particles. This is clearly in contrast to Applicant's claimed invention. Second, the sodium acetate as a pore forming agent is used for preparation of tablets, pressed disks and other oral formulations. The '946 patent does not suggest that sodium acetate or other pore forming agents be used in formulating percutaneous absorption adhesive preparations including a sufficient ion-pair formation as are claimed by Applicant.

Therefore, in summary, neither of the '374 and the '157 patents describe the use of sodium acetate in powder form or having the correct critical size range (as admitted by the

Examiner). The '946 patent does not supply the missing element from Applicant's claimed invention, because the '946 patent teaches the use of sodium acetate as a pore forming agent that is removed to create pores in the coating of a tablet, not in combination with an active ingredient as part of a percutaneous absorption adhesive preparation. One of ordinary skill in the art would not be able or even motivated to determine the particle size of sodium acetate for use in Applicant's compositions for forming a sufficient ion-pair formation based on the teachings of the '946 patent, nor the other two cited patents.

In view of the foregoing arguments, Applicant asserts that the cited prior art patents, alone or in combination, do not teach or suggest the claimed invention. Accordingly, Applicant respectfully requests that the Examiner reconsider withdraw the rejection of the claims under 35 U.S.C. 103.

CONCLUSION

In view of the foregoing remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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